Hematopoietic stem cell quiescence promotes error-prone DNA repair and mutagenesis.

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Public Summary:
Most adult stem cells, including hematopoietic stem cells (HSCs), are maintained in a quiescent or resting state in vivo. Quiescence is widely considered to be an essential protective mechanism for stem cells that minimizes endogenous stress caused by cellular respiration and DNA replication. Our work demonstrates that HSC quiescence can also have detrimental effects. We found that HSCs survive the killing effect of ionizing radiation (IR) due to enhance expression of pro-survival genes and strong activation of p53-mediated DNA damage response. We show that quiescent and proliferating HSCs are equally radioprotected but use different types of DNA repair mechanisms. We describe how nonhomologous end joining (NHEJ)-mediated DNA repair in quiescent HSCs is associated with acquisition of genomic rearrangements, which can persist in vivo and contribute to hematological abnormalities including loss of function. Our results demonstrate that quiescence is a double-edged sword that renders HSCs intrinsically vulnerable to mutagenesis following DNA damage. Our findings have important implications for cancer biology. They indicate that quiescent stem cells, either normal or cancerous, are particularly prone to acquire mutations, which overturns the current dogma that cancer development absolutely requires cell proliferation. They explain why quiescent leukemia-initiating stem cells (LSC), which currently survive treatment in most leukemia, do in fact represent a dangerous reservoir for additional mutations that can contribute to disease relapse and/or evolution, and stress the urgent need to develop effective anti-LSC therapies. Our results also have direct clinical applications for minimizing the risk of therapy-related leukemia following treatment of solid tumors with cytotoxic agents. By showing that proliferating HSCs have significantly decreased mutation rates, with no associated changes in radioresistance, they suggest that it could be beneficial to induce HSCs to enter the cycle prior to therapy with DNA-damaging agents in order to enhance DNA repair fidelity in HSCs and thus reduce the risk of leukemia development. While this possibility remains to be tested in the clinic using FDA-approved agents such as G-CSF, it offers exciting new directions for limiting the deleterious side effects of cancer treatment. Our findings also have broad biological implications for tissue function. While the DNA repair mechanism used by quiescent HSCs can indeed produce defective cells, it is not detrimental for the organism in evolutionary terms. The blood stem cell system is designed to support the body through its sexually reproductive years, so the genome can be passed along. The ability of quiescent HSCs to survive and quickly undergo DNA repair in response to genotoxic stress supports this goal, and the risk of acquiring enough damaging mutations in these years is minimal. The problem occurs with age, as the cells have spent a lifetime responding to naturally occurring insults and the effects of X-rays, medications and chemotherapies. In this context, the accumulation of NHEJ-mediated DNA misrepair and resultant genomic damages could be a major contributor to the loss of function occurring with age in HSCs and the development of age-related hematological disorders.

Scientific Abstract:
Most adult stem cells, including hematopoietic stem cells (HSCs), are maintained in a quiescent or resting state in vivo. Quiescence is widely considered to be an essential protective mechanism for stem cells that minimizes endogenous stress caused by cellular respiration and DNA replication. We demonstrate that HSC quiescence can also have detrimental effects. We found that HSCs have unique cell-intrinsic mechanisms ensuring their survival in response to ionizing irradiation (IR), which include enhanced prosurvival gene expression and strong activation of p53-mediated DNA damage response. We show that quiescent and proliferating HSCs are equally radioprotected but use different types of DNA repair mechanisms. We describe how nonhomologous end joining (NHEJ)-mediated DNA repair in quiescent HSCs is associated with acquisition of genomic rearrangements, which can persist in vivo and contribute to hematopoietic abnormalities. Our results demonstrate that quiescence is a double-edged sword that renders HSCs intrinsically vulnerable to mutagenesis following DNA damage.

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